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The Statistical Comparison of Relative Survival Rates

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SUMMARY

A statistical procedure for comparing the survival of two or more groups of patients adjusted for normal mortality expectation, i.e. for calculating relative survival, is proposed. The method is shown to correspond to some commonly used procedures for comparing unadjusted survival; it provides an improvement over these procedures in many situations, even when the normal mortality expectations for the patient groups are the same. An example of its use is given.

1. Introduction

A number of statistical techniques have been proposed for the comparison of survival experiences among two or more groups of patients diagnosed as having a specific disease (Gehan, 1965; Mantel, 1966; Breslow, 1970; Cox, 1972; Gross and Clark, 1975). These statistical comparisons are often based upon mortality from any cause of death, whether or not related to the disease under study. This is due to the fact that accurate information on cause of death is not available in many instances although time of death is known. In medical follow-up studies, this observed overall survival experience is often inadequate when the primary interest is in mortality associated with a specific disease: not all of the deaths among the patients are associated with the specific disease, and mortality due to other causes may differ among the comparison groups, thus biasing any analysis based upon overall survival. Therefore, to obtain a measure of disease-specific survival, the observed overall survival experience should be corrected for this extraneous mortality.

Two approaches for making this correction have been proposed, based on (i) the theory of competing risks of death (Chiang, 1968; David and Moeschberger, 1978; Prentice *et al.*, 1978), and (ii) the relative survival rate (Ederer, Axtell and Cutler, 1961; Axtell, Asire and Myers, 1976; Hakulinen *et al.*, 1981). The former approach can be used if accurate information on the cause of death of individual patients is available, whereas the latter does not require knowledge of individual causes of death but adjusts the observed survival of each group of patients by a correction factor based on 'normal' or expected general population mortality rates.

Statistical techniques based on the theory of competing risks are well established, however the statistical comparison of survival experiences corrected for extraneous mortality by the relative survival method has not been as well developed. The purpose of this paper is to present a statistical procedure that is based on the relative survival concept but is in the spirit of some of the methods for the comparison of overall survival.

2. The Relative Survival Rate

The relative survival rate, as defined by Ederer *et al.* (1961), is the ratio of the observed overall probability of survival in the patient group, to that expected in a sample of individuals from the general population which is similar to the group of patients at the beginning of the

Key words: Relative survival rate; Score statistics; Survival analysis.

follow-up period with respect to possible factors affecting survival, with the exception of the disease under study. The relevant factors normally taken into account are age, race, sex, calendar period of observation, and domicile. Thus the relative survival rate, often referred to as 'the survival rate adjusted for normal life expectancy', is not actually a rate but, for rare diseases, will approximate the ratio of two probabilities, pr(survival | disease)/pr(survival | no disease). This relative rate has been interpreted as the probability of survival until the end of the follow-up period, provided that the only cause of death is the disease under study. This interpretation is based on the assumption that the patients are subject to two independent forces of mortality: (i) that associated with the specific disease under study, and (ii) that due to all other possible causes of death. In the context of competing-risk theory, the relative rate corresponds to the 'net' probability of survival, given that causes of death associated with the disease are the only risks acting on the population of patients (Chiang, 1968). So, in the following discussion we shall use the term 'relative survival probability' to denote this concept.

The computation of a relative survival probability is straightforward. The overall probability of survival is commonly estimated by the life-table method (Kaplan and Meier, 1958; Cutler and Ederer, 1958), and the expected survival probability is obtained from life tables of national or regional-specific mortality statistics. The statistical comparison of the relative survival probabilities for two groups of patients is often based on the approximate standard errors of the relative survival observed at a single point in time (Ederer *et al.*, 1961). For example, the direct method of adjustment, i.e. a weighted average of subgroup-specific relative rates, along with these standard errors was used by Myers and Hankey (1980) to compare cancer-specific relative survival between white and black patients adjusted for age and stage of disease. These statistical comparisons are based on only a single point in time, and do not compare the entire survival experience over a defined follow-up period as is done in the commonly used procedures for comparing overall survival functions. The following sections describe a procedure for comparing the relative survival functions of two or more groups of patients adjusted for normal mortality.

3. Procedure for Comparing Relative Survival

The procedure will be described in terms of the comparison of the survival experience of two patient groups diagnosed with a fatal disease, adjusted for normal mortality expectation; however, the procedure can be easily extended to more than two groups. Suppose that the follow-up period over which this comparison is to be made consists of n non-overlapping time intervals. Let N_{1i} and N_{2i} denote the numbers of patients at risk in the two groups during the ith interval, and let S_{1i} and S_{2i} denote the known survival expectations of the respective groups for this interval (these expectations will commonly be based on the age-, sex-, and race-specific normal mortality rates of the N_{1i} and N_{2i} patients at risk). Also let Q_{1i} and Q_{2i} denote the unknown relative, or 'disease-specific', interval survival probabilities for the two groups. It should be noted that the term 'disease-specific survival' is used in a loose sense to refer to survival after adjustment has been made for the expected normal mortality. The actual disease-specific survival or mortality would require valid information on cause of death. Under the assumption of independent forces of mortality, the probabilities of escaping mortality from any cause of death during the ith interval are $Q_{ji}S_{ji}$, $j = 1, 2$.

This proposed methodology, like a number of statistical methods that compare survival (Mantel, 1966; Cox, 1972), assumes that the odds ratios of the relative survival probabilities within intervals are constant over time:

$$R = \frac{Q_{2i}(1 - Q_{1i})}{(1 - Q_{2i})Q_{1i}}, \qquad i = 1, \ldots, n. \tag{1}$$

If the time intervals are short, this odds ratio should closely approximate the ratio of the two disease-specific hazard rates, $(1 - Q_{1i})/(1 - Q_{2i})$, since $Q_{2i}/Q_{1i} \sim 1$ for short intervals.

Let $Q_i = Q_{1i}$ denote relative survival probability within an interval for Patient Group 1, then, from (1), $Q_{2i} = RQ_i/\{1 - Q_i(1 - R)\}$. The observed numbers of deaths in the two groups during the ith time interval, denoted by X_{1i} and X_{2i}, are binomially distributed random varibles with parameters $(N_{1i}, 1 - Q_{1i}S_{1i})$ and $(N_{2i}, 1 - Q_{2i}S_{2i})$, respectively.

Under the assumption that the forces of mortality are independent of the censoring mechanism (i.e. in medical follow-up studies, individuals can be censored for a number of reasons including being withdrawn alive or lost to follow-up before the end of the study follow-up period), then the logarithm of the partial likelihood (Cox, 1975) of (X_{1i}, X_{2i}) up to an additive constant is

$$\log L_i = X_{1i} \log (1 - Q_iS_{1i}) + (N_{1i} - X_{1i}) \log (Q_iS_{1i}) + X_{2i} \log \left\{ \frac{1 - Q_i(1 - R + RS_{2i})}{1 - Q_i(1 - R)} \right\} + (N_{2i} - X_{2i}) \log \left\{ \frac{Q_iRS_{2i}}{1 - Q_i(1 - R)} \right\},$$

and the log partial likelihood of the observed data over the entire follow-up period is

$$\log L = \sum_{i=1}^{n} \log L_i. \tag{2}$$

The null hypothesis to be tested is that the interval-relative survival probabilities, $Q_{1i} = Q_{2i}$, $i = 1, \ldots, n$, are equal or, in terms of the assumed constant odds ratio, H_0: $R = 1$. To test this null hypothesis we shall use the method based on score statistics (Cox and Hinkley, 1974, pp. 323–325) which are calculated from partial derivatives of the log likelihood function.

The likelihood function in (2) contains $n + 1$ parameters, namely, the parameter of interest, R, and n nuisance parameters, $0 \leqslant Q_i \leqslant 1$, $i = 1, \ldots, n$. The score statistic for R is

$$S(R) = \left. \frac{\partial \log L}{\partial R} \right|_{R=1, Q_i=\hat{Q}_i}, \tag{3}$$

where the nuisance parameters Q_i, $i = 1, \ldots, n$, are estimated by the maximum likelihood method of solving the nonlinear equations

$$S(Q_i) = \frac{\partial \log L}{\partial Q_i} = \frac{\partial \log L_i}{\partial Q_i} = 0, \qquad i = 1, \ldots, n, \tag{4}$$

under the null hypothesis H_0: $R = 1$. Under this null hypothesis the equations in (4) are quadratic,

$$S(Q_i) = \frac{N_{1i}(1 - Q_iS_{1i}) - X_{1i}}{Q_i(1 - Q_iS_{1i})} + \frac{N_{2i}(1 - Q_iS_{2i}) - X_{2i}}{Q_i(1 - Q_iS_{2i})} = 0,$$

and have the two roots

$$Q_i = \frac{-b_i \pm (b_i^2 - 4a_ic_i)^{\frac{1}{2}}}{2a_i},$$

where

$$a_i = (N_{1i} + N_{2i})S_{1i}S_{2i},$$

$$b_i = X_{1i}S_{2i} + X_{2i}S_{1i} - (N_{1i} + N_{2i})(S_{1i} + S_{2i}),$$

$$c_i = (N_{1i} + N_{2i}) - (X_{1i} + X_{2i}).$$

It can be shown that only one root will be no larger than $\min_j(1/S_{ji})$, and thus use of this root will insure that the overall survival-probability estimates, $\hat{Q}_iS_{1i}$ and $\hat{Q}_iS_{2i}$, will be properly bounded by zero and unity. However, when the observed number of deaths in the

two groups combined is smaller than would be expected from normal mortality, this root will exceed unity. In this case the value of $\hat{Q}_1$ in [0, 1] that maximizes the likelihood will occur on the boundary $\hat{Q}_i = 1$ since the partial derivative $S(\hat{Q}_i = 1)$ will be positive, denoting an increasing likelihood at this boundary.

The score statistic in (3) can be written as

$$S(R) = \sum_{i=1}^{n} \frac{(1 - \hat{Q}_i)}{(1 - \hat{Q}_i S_{2i})} \{N_{2i}(1 - \hat{Q}_i S_{2i}) - X_{2i}\}$$

$$= \sum_{i=1}^{n} \frac{(1 - \hat{Q}_i)}{(1 - \hat{Q}_i S_{1i})} \{X_{1i} - (1 - \hat{Q}_i S_{1i}) N_{1i}\};$$

this represents a weighted sum of the deviations between the observed number of deaths, X_{2i}, in Group 2 and the expected (under H_0) number of deaths, $N_{2i}(1 - \hat{Q}_i S_{2i})$. The weights $W_i = (1 - \hat{Q}_i)/(1 - \hat{Q}_i S_{2i})$ can be interpreted as the ratio of the estimated disease-specific probability of death to the estimated overall probability of death in Group 2. In the case of small probabilities, during the ith interval these weights would correspond to the estimated proportion of deaths in Group 2 attributable to the specific disease; the greater this proportion, the greater the weight given to the deviation between observed and expected numbers of deaths. It should be noted that these weights are 'optimal' in the sense of asymptotic local efficiency for testing against alternative hypotheses of the form given by Equation (1), Cox and Hinkley (1974, p. 113).

Let the information matrix for $(R, Q_1, \ldots, Q_n)'$ be denoted by

$$\mathbf{I} = \begin{bmatrix} I_{RR} & I_{RQ} \\ I_{QR} & I_{QQ} \end{bmatrix}.$$

Then, under H_0: $R = 1$, the estimted asymptotic variance of $S(R)$, conditional on the overall pattern of deaths and censoring, is given by

$$\begin{aligned} \text{var}\{S(R)\} &= I_{RR} - I_{RQ} I_{QQ}^{-1} I_{QR} \\ &= \sum_{i=1}^{n} \left[\frac{N_{2i}(1 - \hat{Q}_i)^2 \hat{Q}_i S_{2i}}{1 - \hat{Q}_i S_{2i}} - \frac{\hat{Q}_i \{N_{2i}(1 - \hat{Q}_i) S_{2i}/(1 - \hat{Q}_i S_{2i})\}^2}{\{N_{1i} S_{1i}/(1 - \hat{Q}_i S_{1i})\} + \{N_{2i} S_{2i}/(1 - \hat{Q}_i S_{2i})\}} \right] \\ &= \sum_{i=1}^{n} \left\{ \frac{N_{1i} N_{2i} S_{1i} S_{2i} \hat{Q}_i (1 - \hat{Q}_i)^2}{N_{1i} S_{1i}(1 - \hat{Q}_i S_{2i}) + N_{2i} S_{2i}(1 - \hat{Q}_i S_{1i})} \right\}. \end{aligned}$$

Therefore, since $\text{E}\{S(R)\} = 0$ under H_0: $R = 1$, a statistical test of the null hypothesis can be based on the statistic

$$T = \frac{S(R)}{[\text{var}\{S(R)\}]^{\frac{1}{2}}}, \tag{5}$$

which will have approximately a standard normal distribution under the null hypothesis.

For comparing the overall survival experience between two groups, the statistic in (5) is nearly equivalent to the logrank statistic of Mantel (1966), and is exactly equivalent to the score-test statistic developed by Day and Byar (1979). Let $S_{1i} = S_{2i} = 1, \quad i = 1, \ldots, n$, and let $M_i = X_{1i} + X_{2i}$ denote the total number of deaths in the ith interval and let $T_i = N_{1i} + N_{2i}$ denote the total number at risk in that interval. Then $\hat{Q}_i = 1 - (M_i/T_i)$ and

$$S(R) = \sum_{i=1}^{n} \{(N_{2i} M_i / T_i) - X_{2i}\},$$

and

$$\text{var}\{S(R)\} = \sum_{i=1}^{n} N_{1i} N_{2i} M_i (T_i - M_i)/T_i^3.$$

The only difference between this statistic and Mantel's statistic is in the computation of $\text{var}\{S(R)\}$, T_i^3 being used in place of $T_i^2(T_i - 1)$.

In the more general case in which $S_{1i} = S_{2i} = S_i$ but is not necessarily equal to unity, the score statistic is a weighted sum of Mantel's deviations, $(N_{2i}M_i/T_i) - X_{2i}$, where the weights are $W_i = (1 - \hat{Q}_i)/(1 - \hat{Q}_i S_i)$ and $\hat{Q}_i = \min[1, \{1 - (M_i/T_i)\}/S_i]$. Since the Mantel statistic weights all the deviations equally, this procedure will produce a larger value for the test statistic when the weights are such that more weight is given to the larger deviations. This will occur in several applications since for many diseases, most notably cancer, the weights will decline with time, and the deviations should be greater in the earlier time periods when more individuals are at risk (decreasing disease-specific hazard rates will accentuate this decreasing trend in the deviations).

Following Mantel's method for adjusting the statistical analysis for the possible confounding effects of other covariate information (e.g. stage of disease which may have a different distribution between the two patient groups), stratification and the combination of summary statistics across the strata can be incorporated into the procedure. For each stratum, $j = 1, \ldots, M$, a score statistic $S_j(R)$ and its variance $\text{var}\{S_j(R)\}$ can be calculated by the method already described. On combining the statistics across the strata, a stratification-analysis statistic becomes

$$T = \sum_{j=1}^{M} S_j(R) \Big/ \left[\sum_{j=1}^{M} \text{var}\{S_j(R)\} \right]^{\frac{1}{2}}.$$

This procedure can also be generalized to a comparison among $G > 2$ groups by assuming $G - 1$ relative survival odds ratios,

$$R_{k-1} = \frac{Q_{ki}(1 - Q_{1i})}{(1 - Q_{ki})Q_{1i}}, \qquad k = 2, \ldots, G.$$

In this situation, the score statistics $S(R_k)$, $k = 1, \ldots, G - 1$, will have a $(G - 1) \times (G - 1)$ covariance structure Σ_R, and a chi square test statistic with multiple degrees of freedom can be formed for testing the equality of the G relative survival experiences. In addition, the equations (4) for estimating the nuisance parameter will become Gth-order polynomials with multiple roots (however, only the smallest root will produce valid estimates of overall survival).

4. Example

We now give an example of the use of this procedure. This example compares the five-year survival experiences of white and black male patients diagnosed as having Hodgkin's disease during the period 1964–1973. The data come from two cancer registries: the California Tumor Registry and the Charity Hospital of New Orleans, which were both participants in the End Results Program of the National Cancer Institute. This example is from the more comprehensive white–black cancer survival analysis by Myers and Hankey (1980).

Table 1 shows the numbers of patients at the beginning of each one-year time interval over the five-year follow-up period; it also shows the numbers of deaths and the numbers of patients censored during each interval, and the normal survival expectation during the time interval for the white and black patients. The normal survival expectation is based on U.S. age-, race-, sex-, calendar-year-specific mortality rates from all causes of death. To adjust for the effect of censoring upon the analysis, we use, as the number of patients at risk during an interval, the number who were alive at the start of the interval minus one-half of those who were censored during the interval.

Table 2 shows the interval calculations and the final values of the test statistic. The estimated (under the null hypothesis of no white–black difference) disease-specific yearly conditional survival probabilities are seen to increase from 80.7% during the first year to 94%

Table 1

Life table for white and black male patients diagnosed as having Hodgkin's disease during 1964–1973

Years after diagnosis	White patients				Black patients			
	L	*D*	*W*	*S*	*L*	*D*	*W*	*S*
0–1	1251	251	7	.9879	119	26	2	.9833
1–2	993	114	5	.9919	91	14	1	.9863
2–3	874	66	17	.9927	76	11	0	.9867
3–4	791	57	45	.9932	65	7	2	.9873
4–5	689	41	99	.9938	56	5	5	.9876

L, number of patients alive at beginning of time interval; *D*, number of patients who died during time interval; *W*, number of patients withdrawn alive (censored) during time interval; *S*, 'normal' interval survival rate of patients alive at start of interval.

during the fifth year. The weights which are applied to the interval-specific deviations between the observed and expected numbers of deaths in the group of black patients (Group 2) are seen to decrease as expected. The test statistic value of $T = -1.83$ indicates that the black patients have a lower disease-specific five-year survival rate than do the white patients, however the difference does not attain statistical significance at the 5% level (two-sided P-value = .067). The score-test statistic, unadjusted for normal survival, yields $T = -2.2$ (P-value = .028). As a comparison, the statistical test used by Myers and Hankey (1980), though not strictly comparable, yields a P-value of .046. The difference between the adjusted and unadjusted test statistics comes from the fact that the normal survival expectation for the white patients is better than that for the black patients, as shown in Table 1. This difference in normal survival is not due to an age difference between the patient groups since the median ages are within one year of each other.

The one-year time intervals used in this example were chosen for illustrative purposes. If the alternative hypothesis of interest concerns the ratio of disease-specific hazard rates, rather than the odds ratio of yearly mortality or survival rates, then shorter time intervals (e.g. one-month intervals) should be used since the odds ratio will closely approximate the ratio of hazard rates. One-monthly intervals were also used for this example and gave substantially similar results.

5. Discussion

The procedure proposed for the comparison of survival between two or more groups of patients adjusted for normal mortality corresponds closely, but not exactly, to the problem of

Table 2

Computations for test statistic comparing survival of white and black patients adjusted for normal survival

Interval	Estimated disease-specific survival	Deviation of (Expected − Observed) number of deaths among black patients	Test statistic weight	Variance of (Expected − Observed) deaths
0–1	.807	−1.665	.935	15.45
1–2	.889	−2.881	.901	7.28
2–3	.926	−4.419	.858	4.09
3–4	.930	−1.765	.856	3.27
4–5	.940	−1.168	.837	2.32

$$T = \frac{\sum W_i(\text{Expected} - \text{Observed})_i}{(\sum \text{var}_i)^{\frac{1}{2}}} = \frac{-10.433}{(32.41)^{\frac{1}{2}}} = -1.83$$

comparing two relative survival probabilities. The relative survival probability is determined at a single point in time. This probability is the ratio of the observed overall probability of survival to the expected survival probability of the patient cohort when subject only to normal mortality. This cohort is defined at the start of the follow-up period, and the expected survival probability for the cohort is an average of the expected survival probabilities for each individual member. Our procedure, however, employs this average expected survival for those members of the patient cohort who are alive at the start of each time interval, i.e. interval-specific conditional relative survival probabilities. Therefore, in terms of competing-risk theory, our procedure could be considered as a method for comparing the net probabilities of survival from only disease-specific causes of mortality (Chiang, 1968).

It should be noted that the product of these interval-specific conditional relative survival probabilities over the follow-up period will not necessarily equal the relative survival for the entire period. Hakulinen (1977) noted that this product method is conceptually different from the idea of relative survival over the entire follow-up period, and will often produce different results since the observed survival will affect the expected survival rates in the product method.

However, this procedure for adjusting the statistical comparison of disease-specific patient survival should provide an improvement over current methods. In the case of differential survival from all causes of death, the adjustment will remove bias which favors the patient group having the better expected survival. In the case of nondifferential normal survival, the adjustment procedure should also provide an improvement over the corresponding procedures for comparing overall survival. Since the comparison of interest is normally concerned with differences in mortality associated with the disease under study, the proposed procedure focuses on alternative hypotheses concerning the ratio of the disease-specific hazard rates, $(1 - Q_{1i})/(1 - Q_{2i}) = R$, whereas the logrank statistic for comparing mortality from any cause of death focuses on alternatives that are confounded with normal mortality, i.e. approximately the ratio of overall hazard rates, $\{(1 - Q_{1i}) + D_i\}/\{(1 - Q_{2i}) + D_i\} = R$, where $D_i = 1 - S_i$ represents the presumed equal normal mortality. However, the two procedures should produce comparable results when the mortality associated with disease is substantially greater than the mortality not associated with the disease.

Buckley (1984) has proposed a similar approach based on a model of hazard rates in which a disease-specific hazard is assumed to be additive to a normal mortality hazard. His maximum likelihood method requires an iterative solution which is not necessary for the approach presented here.

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Résumé

Ce papier propose une méthode de comparaison de la survie de deux ou plusieurs groupes, ajustée pour la mortalité toutes causes (taux relatifs). On montre que cette méthode correspond à quelques procédés largement utilisés de comparaison de survie non ajustée et que dans de nombreuses situations elle constitue une amélioration par rapport à ce procédé, même si les mortalités toutes causes sont les mêmes dans les divers groupes. Un exemple d'application est donné.

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